22 Misdiagnosis of cystic fibrosis in adulthood

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Objectives: Cystic fibrosis (CF) is no longer a disease of childhood. Increased survival of patients with classic CF and emergence of different clinical forms of presentation, adults physicians need to attend those forms.
Describe clinical forms that led to the diagnosis in adults, analyze nutritional status, genetics, pulmonary and pancreatic suffiency.
Methods: This study is retrospective, observational and descriptive of 17 adult patients (4 women and 13 men), with an age range between 18 and 61 years at diagnosis and 30±9.87 average. From a total of 77 patients seen by an interdisciplinary team at the Department of Adult Cystic Fibrosis.
The genetic diagnosis was detected 2 mutations in 6 patients. Sweat test was diagnosed in 11 patients.
Spirometry: FEV_1 averaged 62.48±1.37%.
In all patients chest CT showed bilateral bronchiectasis and air trapping.
Bacteriological examination: *Pseudomonas aeruginosa* (12), methicillin-sensitive *Staphylococcus aureus* (8), methicillin-resistant *Staphylococcus aureus* (6), *Burkholderia cepacia* (1).
Pancreatic involvement: 15 were pancreatic sufficient.
Nutritional status assessed by BMI was between 26.4 and 20.8 with an average of 23.
Previous diagnosis were:
– Bronchitis, pneumonia, asthma and bronchiectasis: 12
– Chronic diarrhea – Bowel obstruction: 9
– Rhinosinusal Disease: 3
– Infertility: 3
– Family screening: 2
Conclusion: CF can be diagnosed at any age and its presentation differ from the classic appearance, this clinical variability can lead to misdiagnosis if not suspected.

23 Diagnosis of cystic fibrosis in a patient carrying the cystic fibrosis transmembrane conductance regulator 186−8T/C allele

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186–8T/C mutation (c.54–8T/C) in intron 1 of the CFTR gene has never been reported to our knowledge. It was identified in a 38 years old Italian woman who referred to our Center for evaluation because she was treated as CF since 2010 following diagnosis based on repeated sweat tests chloride 60 and 74 mEq/L (normal values <50 mEq/L, at the reference clinic) and clinical history consistent with CF; no mutations were identified by first level genetic analysis; small interstitial-alveolar infiltration were evident in CT scan.
The variant 186–8T/C was identified by sequencing. Afterwards the patient referred to our center for assessing the relevance of these findings. Sweat chloride there was 35 and 57 mEq/L. Nasal potential difference (NPD) measurements were therefore performed with results in the normal range.
We hypothesized that the genetic variant 186–8T/C could affect splicing: the same fragments as in healthy donor were amplified by RT-PCR amplified.
Moreover CFTR function was tested by single cell fluorescence analysis (Sorio et al. 2011) in leukocytes: tracings were overlapping with healthy donors. This method is easier for patients and for investigators than currently available and standardized procedures. Simplified and feasible functional assays in leukocytes are under investigation in order to provide an additional tool for investigating genetic variants of uncertain clinical relevance as well as the effects of drugs targeting the CF basic defect.
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24 ENaC-related disorder as a new CF-like clinical entity

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Background: Significant proportion of CF-like patients, who enter CF diagnostic algorithm end in intermediate categories between CF unlikely, *CFTR*-related disorder and CF. Transheterozygosity for ENaC/*CFTR* variants may lead to deficient ENaC/CFTR interaction, abnormal ion transport and CF-like disease, but mechanism of relation between CFTR and ENaC are not well described.
Aim of this study was to evaluate correlation between phenotype, *CFTR*/ENaC genotype and channels functionality.
Methods: A total of 51 subjects (53% female, mean age: 16.6, range 6–28 years) with inconclusive CF diagnosis were investigated by nasal potential difference (NPD: ENaC-hyperactivity = DPD_{Ami} >17 mV; CFTR dysfunction $DPD_{0Cl-+Iso}$ <−8 mV), sweat test, *CFTR* genotyping (sequencing+MLPA) and sequencing of coding regions of ENaC genes (*SCNN1A*, *SCNN1B*, *SCNN1G*).
Results: Subjects were classified as: CF unlikely without ENaC-hyperactivity (n = 24), CF unlikely with ENaC-hyperactivity (n = 7), *CFTR*-related disorder (n = 6), PS-CF (n = 4), PI-CF (n = 4) and ENaC-related disorder independent of *CFTR* mutations/dysfunction as a new CF-like clinical entity (n = 6).
Conclusions: This study provides growing evidence of a new "CF-like" diagnostic category with ENaC-hyperactivity caused by ENaC mutations. CFTR/ENaC function can be directly measured and separated by NPD, whereas sweat test alone does not distinguish between ENaC hyperactivity and CFTR dysfunction. ENaC-related disorder seems to be an underestimated cause of CF-like disease, and reference values and diagnostic categories are in need of a differentiated update.
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25 Analysis of *CFTR* gene mutations in Portuguese patients with idiopathic bronchiectasis

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Introduction: CF is *characterized* by recurrent *lung* infections, malabsorption, malnutrition, and male infertility. Some patients with bronquiectasis and without other clinical features of CF have been associated with mutations in the *CFTR* gene. The main objective of this work was to analyze the profile of *CFTR* mutations in adult patients diagnosed with idiopathic bronquiectasis.
Patients and Method: Thirty-six Portuguese patients with isolated bronquiectasis were screened for the 33 most frequent *CFTR* mutations in the Caucasian population using the OLA CFTR kit (Abbott) and for the IVS8(TG)mTn variants. In those patients with only one or no mutations identified, the *CFTR* gene sequencing and MLPA analysis were performed.
Results: Four different mutations were identified, F508del, R334W, V754M and IVS8T5. From the 36 patients, 2 (5%) had 2 mutations and 6 (17%) had 1 mutation. The most frequent mutation detected was the IVS8–5T, detected with an allelic frequency of 10% and it is associated with the IVS8TG12 repeats in 57% of the cases.
Conclusions: Eight (22%) patients had at least one *CFTR* mutation, which is significantly higher than the percentage reported for the general population (4%). The allelic frequency of the IVS8T5 variant was 10%, also higher than the one reported for the Caucasian population (5%). The IVS8T5 variant seems to have an important role in cases of idiopathic bronquiectasis. This is similar to that reported for CFTR related disorders such as congenital absence of the vas deferens. The results of this study highlight the importance of *CFTR* gene screening, including the analysis of IVS8TGmTn variants in patients with idiophatic bronquiectasis.